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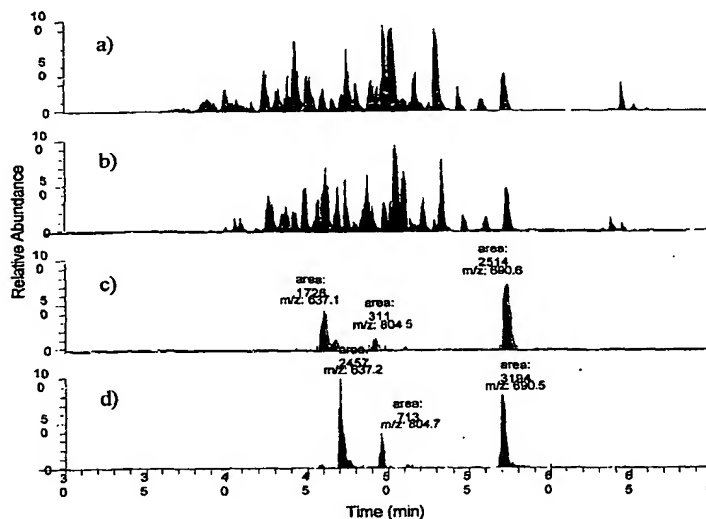
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19 August 2004

[Continued on next page]

(54) Title: **QUANTITATION OF BIOLOGICAL MOLECULES**



(57) Abstract: Methods and apparatus, including computer program products, for quantifying peptides in a peptide mixture. A peptide mixture containing a plurality of peptides is received. One or more peptides are separated from the peptide mixture over a period of time. One or more of the peptides separated at a particular time are subjected to mass-to-charge analysis and an abundance of one or more of the mass analyzed peptides is calculated. A relative quantity for the one or more mass analyzed peptides is calculated by comparing the calculated abundance of the peptides with an abundance of one or more peptides in a reference sample that is external to the first peptide mixture. The techniques can be applied to arbitrary peptides, without requiring the use of differential mass labeling, and can be applied to other biological molecules, such as nucleic acids and small molecules.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/11870

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 G01N33/68 H01J49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 G01N H01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| P,X | CHELIUS DIRK ET AL: "Analysis of the adenovirus type 5 proteome by liquid chromatography and tandem mass spectrometry methods." JOURNAL OF PROTEOME RESEARCH, vol. 1, no. 6, pages 501-513, XP002270551 ISSN: 1535-3893 (ISSN print) page 502 -page 504; figures 3,4 | 1-41 |
| P,X | CHELIUS DIRK ET AL: "Capture of peptides with N-terminal serine and threonine: A sequence-specific chemical method for peptide mixture simplification." BIOCONJUGATE CHEMISTRY, vol. 14, no. 1, pages 205-211, XP002270552 ISSN: 1043-1802 (ISSN print) page 205 -page 208; figures 3-6 -/- | 1-41 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & document member of the same patent family

Date of the actual completion of the international search

17 February 2004

Date of mailing of the international search report

05/03/2004

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GONCALVES M L F C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/11870

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|---|
| P,X | CHELIUS DIRK ET AL: "Quantitative profiling of proteins in complex mixtures using liquid chromatography and mass spectrometry" JOURNAL OF PROTEOME RESEARCH, vol. 1, no. 4, 6 June 2002 (2002-06-06) - July 2002 (2002-07), pages 317-323, XP002270553 ISSN: 1535-3893 page 318 -page 323; figures 3,4 | 1-41 |
| P,X | CHELIUS DIRK ET AL: "Identification of N-linked oligosaccharides of rat insulin-like growth factor binding protein-4" GROWTH HORMONE AND IGF RESEARCH, vol. 12, no. 3, June 2002 (2002-06), pages 169-177, XP009026066 ISSN: 1096-6374 | 1-9, 13-16, 18-22, 24-36, 38,39 |
| A | abstract | 10-12, 17,23, 37,40,41 |
| X | US 6 011 259 A (DRESCH THOMAS ET AL) 4 January 2000 (2000-01-04) | 1-9, 13-16, 18-22, 24-36, 38,39 |
| A | abstract; claims | 10-12, 17,23, 37,40,41 |
| X | GYGI S P ET AL: "QUANTITATIVE ANALYSIS OF COMPLEX PROTEIN MIXTURES USING ISOTOPE-CODED AFFINITY TAGS" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 17, no. 10, October 1999 (1999-10), pages 994-999, XP001010578 ISSN: 1087-0156 page 995 -page 996; figures 2,3 | 1-41 |
| A | WO 01 84143 A (THERMO FINNIGAN LLC ;JARDINE IAN (US); LADINE JAMES R (US); STORY) 8 November 2001 (2001-11-08) page 6 -page 18 | 1-41 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/11870

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 42, 43
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 42,43

Present claims 42 and 43 relate to an extremely large number of possible "compounds in a biological sample". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the application which appear to be supported and disclosed, namely those parts relating to the "compounds in a biological sample" being "peptides", and is accordingly restricted to the subject-matter of claims 1-41.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/11870

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
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